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ORIGINAL INVESTIGATION

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Abuse liability of flunitrazepam among methadone-maintained patients

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Abstract Abuse liability and acute subjective and psychomotor effects of flunitrazepam were assessed in ten methadone-maintained males with history of benzodiazepine and alcohol use, who voluntarily participated in a double-blind, controlled, cross-over, randomized clinical trial. There were six experimental sessions in which a single oral dose of flunitrazepam 1, 2, and 4 mg; triazolam 0.5 and 0.75 mg; and placebo was given. Evaluations included physiological measures; psychomotor performance tasks (simple reaction time, Digit Symbol Substitution Test, balance task, Maddox-wing device); and self-administered subjective effects questionnaires [Addiction Research Center Inventory (ARCI), Profile of Mood States (POMS), a series of visual analog scales (VAS)]. All drugs but flunitrazepam 1 mg caused an impairment of psychomotor tasks. Effects were more evident with the highest doses of both drugs. Only flunitrazepam 4 mg produced a significant decrease in balance time. Triazolam 0.75 mg induced increases in sedation measured by ARCI-PCAG, depression in POMS, and VAS-drowsiness scores. Flunitrazepam 4 mg caused euphoria-related effects as measured by increases in ARCI-MBG and "high" scores in the VAS. Our findings of flunitrazepam-induced euphoria in methadone-maintained subjects together with epidemiological evidence of flunitrazepam abuse by opioid dependents, suggest that it may be included in the group of benzodiazepines with a relatively high abuse potential.

Key words Flunitrazepam · Benzodiazepine · Methadone · Abuse liability · Opioid abuse

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Introduction

Benzodiazepines are commonly abused by drug addicts. In a sample of heroin addicts admitted for inpatient detoxification, 68.5% were consuming benzodiazepines at the time of admission and almost half used benzodiazepines on a daily basis (San et al. 1993a). Data from different opioid dependence treatment centers have shown that as many as 50–70% of patients are likely to be using and/or abusing benzodiazepines as indicated by positive urine testing (San et al. 1993b). There is also a relatively high rate of abuse of benzodiazepines in patients included in methadone maintenance programs (DuPont 1988; Iguchi et al. 1993).

Flunitrazepam, a hypnotic benzodiazepine marketed in different countries, has recently been shown to be misused among opioid abusers (Navaratnam and Foong 1990; Barnas et al. 1992; San et al. 1993b). It also seems to be the most preferred benzodiazepine in this population. In a sample of opioid dependent subjects, flunitrazepam was not only the favourite benzodiazepine but also the drug that obtained the highest score of liking, followed by diazepam (Darke et al. 1995). In a sample of methadone-maintained patients who ranked their liking for different oral benzodiazepines, flunitrazepam also scored higher than diazepam, triazolam, lorazepam, or oxazepam (Barnas

et al. 1992). Flunitrazepam has recently been associated with health problems in border states of the United States (e.g., Texas) where the drug is purchased in Mexico or smuggled from other countries, and there is a great concern about its use as "party drug" or when used for "date rape" (Calhoum et al. 1996). Flunitrazepam seems to be mainly abused by the oral route, although there are reports of "snorting" (Bond et al. 1994) and IV injection (Darke et al. 1995).

The pharmacological bases (pharmacodynamic or pharmacokinetic) that may explain the preference for this compound are unknown. It has been suggested that the fast onset of drug effects can be a factor contributing to the abuse potential (Farré and Camí 1991). Flunitrazepam is a very lipophilic substance that seems to enter rapidly into the central nervous system (Arendt et al. 1983). Flunitrazepam and other benzodiazepines are used by substance abusers to enhance or boost the effects of heroin, to obtain a better "high" and to prevent or suppress withdrawal symptoms (Stitzer et al. 1981; Navaratnam and Foong 1990).

The clinical abuse potential of flunitrazepam in ex-substance abusers or opioid abusers has not been assessed in experimental studies. In a study in healthy volunteers (Farré et al. 1996), flunitrazepam induced statistically significant increases in some pleasurable-related subjective effects ("liking", "good effects", "high") that may be related to its abuse potential. This study was designed to assess the acute subjective and psychomotor effects of flunitrazepam in methadone-maintained patients. We conducted a randomized clinical trial using triazolam and placebo as control medications. For testing the clinical abuse liability, specific questionnaires, such as the Addiction Research Center Inventory (ARCI) and the "liking" or "high" scales, were used.

Materials and methods

Subjects

Ten white male subjects admitted to a methadone maintenance program voluntarily agreed to be enrolled in the study. Their mean age was 31 years (range 22–40 years), mean weight 64.7 kg (range 59–74.7 kg), and mean height 170.8 cm (range 152–177 cm). Participants were recruited from three methadone clinics (CAS Barceloneta, CAS Garbivent, CAS Creu Roja) in the city of Barcelona. Patients were included if they were admitted to the methadone maintenance program at least 3 weeks before their selection, took methadone at daily doses between 40–50 mg (mean dose 44 mg), and were given the same methadone dose for at least 1 week before the beginning of the study and throughout the study period. They were medication-free, other than methadone during the study. All subjects had a history of sedative-hypnotic (benzodiazepine) and alcohol use. All were cigarette smokers (mean 27 cigarettes/day, range 10–40).

They underwent a full medical examination including 12–lead ECG, complete blood cell count, biochemical profile including serological tests for viral hepatitis, HIV testing, and urinalysis. All participants were found to be in good health, and no other medical conditions and psychiatric disorders other than current opioid dependence according to DSM-III-R criteria were diagnosed. Three subjects were HIV seropositive, but none met the criteria for AIDS diagnosis.

The study protocol was approved by the local Institutional Review Board and the Spanish Ministry of Health (DGFPS 93/247). All volunteers gave their written informed consent prior to inclusion in the study, and were paid for their participation. The study was designed and conducted in accordance with Declaration of Helsinki. In order to avoid the subjective effects of expectancy, subjects were informed that they would receive single doses of stimulants, sedatives, or placebo.

Study design and procedure

Subjects participated as outpatients in one training session and six experimental sessions that were carried out with at least 2-day washout periods. In the first session, that was not blind, subjects received placebo. The purpose of this session was to familiarize volunteers with the testing procedures. During the following six sessions, the study was conducted as a double-blind, controlled, cross-over comparison, and randomized according to a balanced 6×6 Latin-square design. The six drug conditions were as follows: flunitrazepam 1, 2, and 4 mg (Rohipnol, Laboratorios Roche, S.A., Madrid, Spain), triazolam 0.5 and 0.75 mg (Halcion, Upjohn Farmoquímica, Madrid, Spain), and placebo (lactose). The doses of flunitrazepam and triazolam were selected according to previous studies in healthy volunteers (Farré et al. 1996). Drugs were supplied by the Pharmacy Department of Hospital del Mar as identically appearing opaque white soft-gelatin capsules. Two capsules were administered in each experimental session with 120 ml tap water.

Subjects reported to the clinical research unit at 8:00 a.m. after an overnight fast. A light breakfast was provided at 8:15 a.m., the study drug was administered 45 min later, and continuous controls were performed over 6 h after drug administration. Daily methadone doses were given at the end of the session at 15:30 p.m. Evaluations included recording of physiologic measures, psychomotor performance tasks, and self-administration of subjective effects questionnaires. Physiologic measures, psychomotor tasks, and visual analog scales were performed at baseline (pre-drug) and at 0.5, 1, 1.5, 2, 3, 4 and 6 h after drug administration. The 49-item short form of ARCI and the 72-item version of the Profile of Mood States (POMS) were administered at baseline and at 1, 2, 3, 4 and 6 h after drug administration (at 4 h only ARCI was administered). Subjects had a light lunch 5 h after treatment administration. During the sessions volunteers were seated in a chair, they were free to engage in leisure activities of their choice (e.g., watching TV, reading, music listening, talking), but they were not allowed to work, study or sleep. If drug effects were still evident at the end of the session, subjects remained in the unit until effects had disappeared. Urine samples were collected at the beginning of each session for screening of drugs of abuse using an immunoassay (TDx, Abbott, Ann Arbor, Mich., USA).

Physiological measures

Physiological measures included systolic and diastolic blood pressure, heart rate, and oral temperature. They were measured using an automatic device (Dinamap 8100-T, Critikon, Tampa, Fla., USA).

Psychomotor performance tests

The psychomotor performance battery included the simple reaction time, Digit Symbol Substitution Test (DSST), balance task, and

Maddox-wing device which were selected because of their sensitivity to benzodiazepine effects (Hindmarch 1980). Each participant was pretrained on the psychomotor tasks during the first training session in order to achieve steady-performance in simple reaction time and DSST (Farré et al. 1996).

The simple reaction time is a measure of the sensory-motor performance (Hindmarch 1980) and was assessed using the Vienna Reaction Unit (PC/Vienna System, Schufried, Austria). Details of the procedure have been previously described (Farré et al. 1993, 1996). Results were expressed in milliseconds as the mean of the response time to 50 stimuli (simple reaction time).

The DSST, designed to evaluate recognition and recording of visual information (Hindmarch 1980), is a subtest of the Wechsler Adult Intelligence Scale – Revised (Wechsler 1958). A computerised version was used (McLeod et al. 1982). Scores were the number of correct patterns keyed in and the number of patterns attempted in 90 s.

The balance task measured the subject's ability to stand upright on one foot with his eyes closed and arms extended to the side at shoulder height (Evans et al. 1990; Farré et al. 1996). The score for this task was the sum of the time the subject was able to remain in the upright position without touching the raised foot to the floor when tested for 30 s on each foot; maximum possible score was 60 s.

Maddox-wing device measures the balance of extraocular muscles and quantifies exophoria (an indicator of psychomotor impairment) and esophoria, expressed in diopters, along the horizontal scale of the device (Hannington-Kiff 1970).

Subjective effects questionnaires

The subjective effects questionnaires were ARCI (Haertzen 1974), POMS (McNair et al. 1971), and a series of visual analog scales (Farré et al. 1993, 1996). A short form of the ARCI consisting of five scales with a total of 49 items was used (Martin et al. 1971). The five scales were PCAG (pentobarbital-chlorpromazine-alcohol group, a measure of sedation); MBG (morphine-benzedrine group, a measure of euphoria); LSD (lysergic acid dyethylamide scale, a measure of dysphoria and somatic symptoms); BG (benzedrine group, a stimulant scale consisting mainly of items relating to intellectual efficiency and energy); and A scale (amphetamine, an empirically derived scale sensitive to the effects of *d*-amphetamine). A Spanish validated version was administered (Lamas et al. 1994b).

Visual analog scales included a set of 14 horizontal 100-mm lines, each labelled with an adjective ("stimulated", "high (feeling good)", "any effect", "good effects", "bad effects", "liking", "drunken", "drowsiness", "active", "passive", "nervous", "calm", "concentration", "performance"). The left ends of the lines were labelled "not at all" and the right ends "extremely". Subjects were instructed to place a mark on each line indicating how they felt at that moment.

At the end of each study session, subjects filled out a drug class identification questionnaire in which the class of drug they believed had been given (placebo, opioid agonists, opioid antagonists, neuroleptics, barbiturates, benzodiazepines, hallucinogens, amphetamine-like stimulants, cocaine, alcohol, cannabis, and other) was indicated.

A questionnaire, derived from the Himmelsbach opiate withdrawal scale (Kolb and Himmelsbach 1938), was used to assess possible opioid withdrawal symptoms at baseline and at the end of each session.

Statistical analysis

Values from all variables were transformed to changes from baseline measures. The peak effect (maximum absolute change from baseline values) and the 6-h area under the time-effect curve (AUC) calculated by the trapezoidal rule, were determined for each variable. These transformations were analyzed by a one-factor repeated measures analysis of variance (ANOVA) with drug doses as factor. When ANOVA showed significant differences between treatments, post-hoc multiple comparisons were performed using the Tukey's test. Differences associated with P values lower than 0.05 were considered to be significant.

Results

Statistical comparisons of AUC values for each variable are shown in Table 1. Statistical comparisons of peak effects for variables where ANOVA was significant are shown in Figs. 1 and 3.

Physiological measures

With regard to physiologic measures, triazolam 0.75 mg produced a slight increase in heart rate as compared with placebo and flunitrazepam. Only flunitrazepam 4 mg induced a fall in oral temperature with a mean difference of 0.8°C as compared with placebo and 0.5°C as compared with all other treatments. Peak effects are shown in Fig. 1.

Psychomotor performance tests

Both doses of triazolam and flunitrazepam 2 mg and 4 mg significantly impaired the performance of the simple reaction time. Flunitrazepam 4 mg and both doses of triazolam produced a decrease in correct responses of DSST. Only highest doses of both drugs produced a marked exophoria measured by the Maddox-wing device. Only flunitrazepam 4 mg impaired the balance time. Flunitrazepam 1 mg was not different from placebo in any performance tasks. Flunitrazepam 4 mg and triazolam 0.75 mg produced similar impairment of psychomotor tasks followed by triazolam 0.5 mg and by flunitrazepam 2 mg. Figure 2 shows the time-course effects of the drug treatments on DSST and balance. Peak effects results are presented in Fig. 1. The maximal change on performance after triazolam was mainly observed 1–2 h after administration. In the case of flunitrazepam, the maximal impairments on performance tasks were observed between 2 and 3 h after drug administration.

Subjective effects

Although flunitrazepam (2 mg and 4 mg) and both doses of triazolam increased the scores of the PCAG scale of ARCI, only triazolam 0.75 mg produced a significant increase in comparison with placebo (AUC). Only flunitrazepam 4 mg increased ratings of the MBG (euphoria) scale in relation to placebo, flunitrazepam

Table 1 Summary of statistical results of physiological, psychomotor performance and subjective evaluations (area under the curve effect). Abbreviations used are: *P* placebo, *F4* flunitrazepam 4 mg, *F2* flunitrazepam 2 mg, *F1* flunitrazepam 1 mg, *T.75* triazolam 0.75 mg, *T.5* triazolam 0.5 mg, *HR* heart rate, *T* temperature, *SRT* simple reaction time, *F* ANOVA's *F* value (*df* 5,45), *P* level of statistical significance

			Tukey multiple comparison test														
	ANOVA		*P*					F4				F2			F1		T.75
Variable	*F*	*P*	F4	F2	F1	T.75	T.5	F2	F1	T.75	T.5	F1	T.75	T.5	T.75	T.5	T.5
Physiological measures																	
HR	7.50	<0.0001	NS	NS	NS	[b]	[a]	NS	NS	[a]	NS	NS	[b]	NS	[a]	NS	NS
T	4.43	0.0023	[b]	NS	NS	NS	NS	NS	[a]	[a]	[a]	NS	NS	NS	NS	NS	NS
Psychomotor performance																	
SRT	10.13	<0.0001	[b]	NS	NS	[b]	[a]	NS	[b]	NS	NS	NS	[b]	NS	[b]	NS	NS
DSST	7.88	<0.0001	[b]	NS	NS	[b]	NS	[a]	[b]	NS	NS	NS	[a]	NS	[b]	NS	NS
Balance	5.49	0.0005	[b]	NS	NS	NS	NS	[b]	[b]	NS	[a]	NS	NS	NS	NS	NS	NS
Maddox-Wing	6.52	0.0001	[b]	NS	NS	[b]	NS	[a]	[a]	NS	[b]	NS	NS	NS	NS	NS	NS
Subjective effects																	
ARCI																	
PCAG	3.36	0.0115	NS	NS	NS	[a]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
MBG	5.43	0.0005	[b]	NS	NS	NS	NS	NS	[a]	[b]	[b]	NS	NS	NS	NS	NS	NS
POMS																	
Depression	2.62	0.0367	NS	NS	NS	[a]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
VAS																	
High	4.26	0.0029	[b]	NS	NS	NS	NS	NS	[a]	NS	NS	NS	NS	NS	NS	NS	NS
Any effect	6.43	0.0001	[b]	NS	NS	NS	NS	NS	[b]	NS	[b]	NS	NS	NS	NS	NS	NS
Drunken	3.27	0.0133	[a]	NS	NS	NS	NS	NS	[a]	NS	[a]	NS	NS	NS	NS	NS	NS
Drowsiness	3.32	0.0123	NS	NS	NS	[b]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Performance	2.59	0.0386	[a]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Tukey's test statistical significance: [a] $P < 0.05$; [b] $P < 0.01$; *NS* not significant. Only variables that showed statistically significant differences in Tukey test are presented

1 mg, and both triazolam doses. Neither drug increased ratings of the LSD, BG, and A scales in relation to placebo. The time-course and peak effects are shown in Figs. 2 and 3, respectively.

In the POMS questionnaire and in comparison with placebo, the highest doses of flunitrazepam and triazolam caused a statistically significant increase in the scores of anger and depression, respectively.

With regard to the visual analog scales, flunitrazepam 4 mg caused significant increases in the ratings of "high", "any effect", "drunken", and significant decreases in "performance" as compared with placebo (Figs. 2 and 3). Triazolam 0.75 mg produced a significant increase in the ratings of "drowsiness". The effects of flunitrazepam 1 and 2 mg and triazolam 0.50 mg were not significantly different of those observed after the administration of placebo. The maximal effects on subjective variables after the administration of flunitrazepam peaked between 1 and 2 h. After triazolam 0.75 mg, the maximal effects on PCAG and the "drowsiness" scale were observed at 2 and 3 h.

In the pharmacological class identification questionnaire, the administration of placebo was identified as a benzodiazepine (two of ten possible identifications), a stimulant (2/10), and placebo (6/10). Flunitrazepam 4 mg was identified as a benzodiazepine (5/10), stimulant (3/10), opioid agonist (1/10), and placebo (1/10). Triazolam 0.75 mg was considered as a benzodiazepine (7/10), placebo (2/10), and stimulant (1/10). None of the subjects presented symptoms of opioid withdrawal at baseline or during the experimental sessions.

Discussion

Overall, a relatively similar pattern of sedative effects for flunitrazepam and triazolam was found in methadone-maintained patients, but there were differences in some variables related to drug-induced pleasurable or euphoric effects.

With regard to physiologic measures, triazolam 0.75 mg produced a mild increase in heart rate. Different benzodiazepines at therapeutic doses may induce limited effects on physiological parameters (heart rate or blood pressure). This effect is more evident when the drug is administered by the IV route, resulting in an increase or a decrease in these measures (Korttila 1975). In our study, flunitrazepam decreased oral temperature; a similar result was also obtained in healthy volunteers (Farré et al. 1996).

In addition to the sedative effects of the drug, γ-aminobutyric acid (GABA) has been implicated in the control of body temperature (Sancibrian et al. 1991).

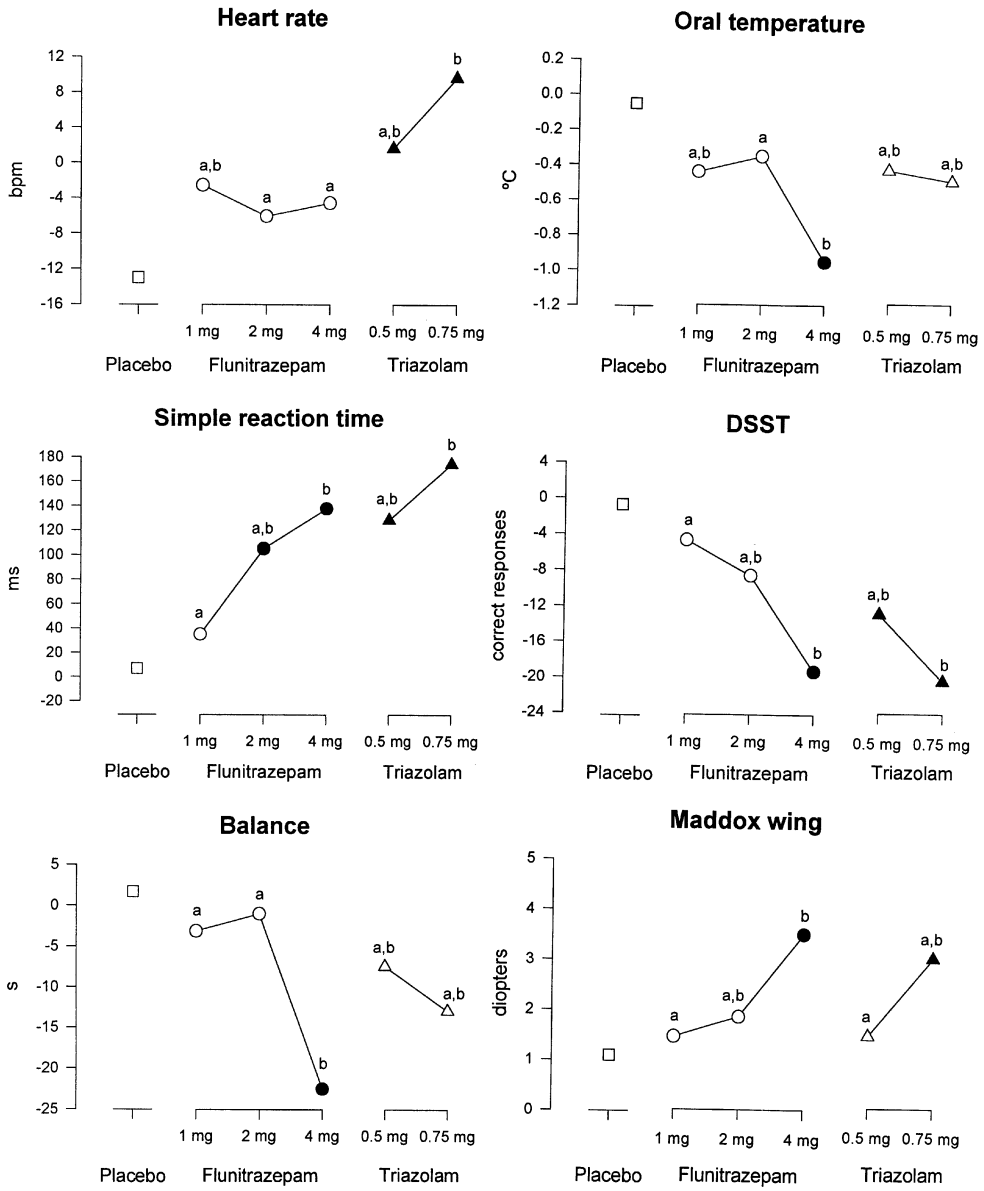

Fig. 1 Peak drug effects on the physiological and psychomotor performance measures (differences from baseline). Data points represent means from ten subjects. *Filled symbols* indicate a significant difference from placebo ($P < 0.05$). Letters *a*, *b* and *c* indicate comparisons among the five drug active doses; within the same panel, any two means designated with the same letter are not significantly different from each other at $P < 0.05$ (Tukey's post hoc tests). Symbols: ○ flunitrazepam, Δ triazolam, □ placebo. Abbreviations: *bpm* beats per minute, *ms* milliseconds, *s* seconds

All study drugs but flunitrazepam 1 mg induced some degree of sedation as measured by objective tests (increases on the simple reaction time), but only triazolam 0.75 mg increased significantly some subjective-related measures of sedation (see below). The highest doses of both drugs also reduced the responses of DSST and induced exophoria. In terms of performance impairment, both flunitrazepam and triazolam seemed similar. In order of potency, flunitrazepam 4 mg and triazolam 0.75 mg produced similar impairment, and produced the greatest sedation followed by triazolam 0.50 mg and flunitrazepam 2 mg. These results are in agreement with other studies in which the effects of these compounds were tested in different populations (Evans et al. 1990; Grahnén et al. 1991; Ingum et al. 1992, 1994; Rush et al. 1993a,b; Farré et al. 1996).

Only flunitrazepam 4 mg impaired the balance task. This finding is consistent with a previous study in which the same study drugs were given to healthy subjects (Farré et al. 1996). However, in the study of Patat et al. (1986), both triazolam and flunitrazepam impaired the body sway. Our balance task failed to detect any difference between placebo and triazolam 0.50 and 0.75 mg, which may be related to the simplicity of the balance measure in comparison to other methods (biomechanics force platforms or posturography) (Patat et al. 1986; Robin et al. 1991).

In relation to subjective effects, although flunitrazepam induced sedation, increases did not reach statistical significance. Only triazolam 0.75 mg produced a statistically significant increase in the subjective measures of sedation (e.g. PCAG of ARCI or "drowsiness"

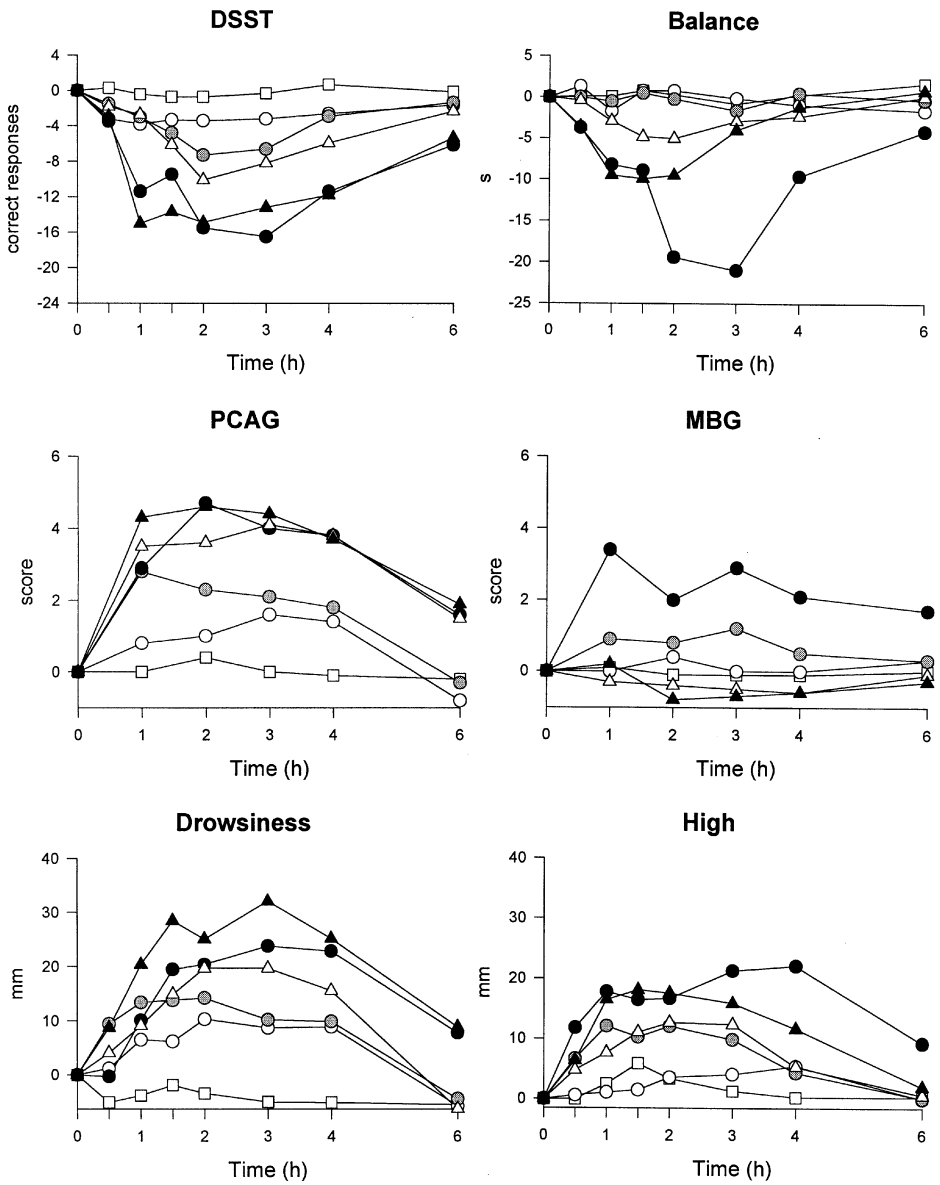

Fig. 2 Time course of drug effects on DSST, balance, ARCI PCAG and MBG scales, and on the "drowsiness" and "high" VAS scores (differences from baseline). Data points represent means from ten subjects. Symbols: ● flunitrazepam 4 mg, ◍ flunitrazepam 2 mg, ○ flunitrazepam 1 mg, ▲ triazolam 0.75 mg, Δ triazolam 0.5 mg, and □ placebo

scores). Flunitrazepam produced noticeable increases in euphoria-related effects as measured by increases in MBG of ARCI or "high" in the visual analog scale. Anger feeling, measured by POMS, only appeared when flunitrazepam 4 mg was administered.

The doses administered were higher than those recommended for hypnotic purposes in ordinary patients by formularies (Association of the British Pharmaceutical Industry 1994; Physician's Desk Reference 1995) (flunitrazepam: 0.5–1 mg, maximum dose 2 mg; triazolam: 0.125–0.25 mg, maximum dose 0.5 mg) but in the range of doses recommended for abuse liability testing (between 2 and 4 times the therapeutic dose) (Evans et al. 1991). However, in Spain and up to 1996, the doses of flunitrazepam recommended ranged from 0.5 to 4 mg (Medicom 1995). It is well known that high doses of drugs are usually required to elicit effects in sedative abusers in comparison to healthy subjects or patients (Evans et al. 1991). According to our results, this relative tolerance seemed to be more intense in the subjective measurements and less marked in psychomotor performance testing. Only the highest doses of both drugs produced differences in subjective effects in comparison to placebo, while flunitrazepam 2 and 4 mg and both doses of triazolam induced clear effects on some performance tasks (reaction time). In a previous study using lower doses of the same drugs in healthy volunteers, a similar pattern of sensitivity was observed (Farré et al. 1996).

A finding relevant to the abuse liability evaluation of flunitrazepam was the observed increase in the MBG scale of ARCI. This scale was originally developed to measure euphoria produced by opioids and amphetamine-like drugs, but other drugs of abuse could increase the score (Haertzen and Hickey 1987). In terms of clinical abuse liability testing, the MBG is considered the

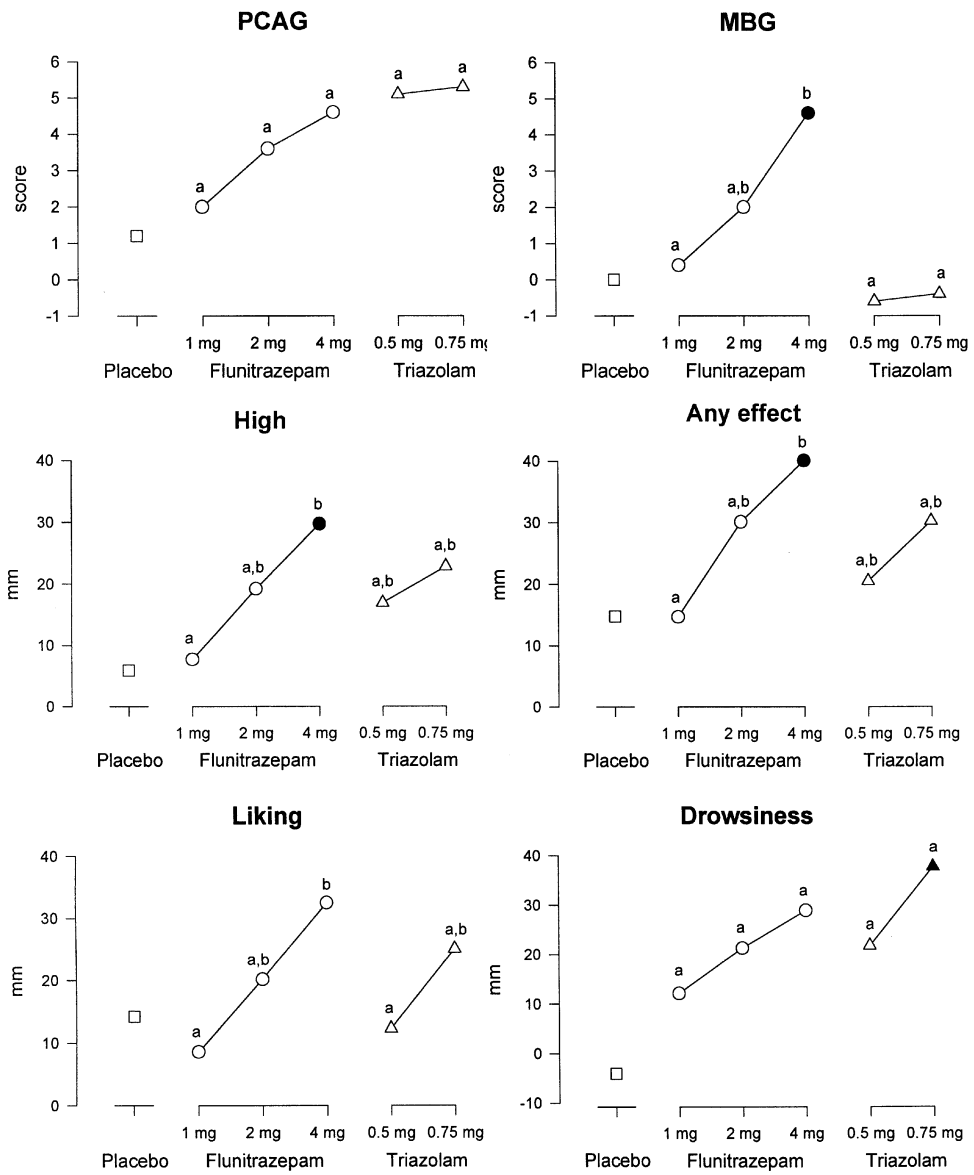

Fig. 3 Peak drug effects on the ARCI PCAG and MBG scales, and on the "high", "any effect", "liking" and "drowsiness" VAS scores (differences from baseline). *Filled symbols* indicate a significant difference from placebo ($P < 0.05$). Letters *a*, *b* and *c* indicate comparisons among the five drug active doses; within the same panel, any two means designated with the same letter are not significantly different from each other at $P < 0.05$ (Tukey's post hoc tests). Symbols: ○ flunitrazepam, Δ triazolam, □ placebo

most direct measure of abuse potential, with a direct relation between the increases and the misuse of substances (Henningfield et al. 1987). Increases in the MBG scores and/or drug "liking", "good effects", and "high" have been described when some benzodiazepines (lorazepam, diazepam, triazolam, or alprazolam) were administered to sedative abusers or to subjects with previous or current history of opiate abuse/dependence (Roache and Griffiths 1985; Preston et al. 1989, 1992; Sullivan et al. 1993; Busto et al. 1994). In healthy volunteers, increased scores of "liking" or drug strength scales were found when flunitrazepam was administered by the oral route (Farré et al. 1996) or snorting (Bond et al. 1994). The euphoria induced by flunitrazepam could reasonably explain its abuse by opioid dependent subjects, its relative preference over other benzodiazepines in countries where the drug is marketed, and the higher liking scores obtained in different epidemiological studies (Barnas et al. 1992; San et al. 1993a; Darke et al. 1995).

In contrast to flunitrazepam, triazolam produced more sedative than pleasurable effects. These results are in agreement with opinions of a moderate abuse potential for triazolam based on experimental observations (Roache and Griffiths 1985; Evans et al. 1990) as well as with data from epidemiological studies(Barnas et al. 1992; Iguchi et al. 1993).

The selection of methadone-maintained patients to evaluate the abuse potential of a sedative drug is a novel contribution of this study. This population has some advantages and disadvantages in comparison with other groups (e.g., healthy subjects, ex-addicts). An important advantage of this approach is that the study was carried out specifically in one of the populations that abuse this class of drugs, which could increase the external validity of the results obtained. The

inclusion of methadone-maintained patients could have some disadvantages. There is the possibility of a drug interaction between the experimental drug (flunitrazepam or triazolam) and methadone. Also, the subjects are evaluated under the effects of methadone, and the possibility of opioid withdrawal symptoms during the experiment should also be excluded. It is difficult to recruit patients. They must have willingness to participate, be in relative good health, stabilized in a narrow maintenance dose range, and not taking any drug of abuse or medication concomitantly. Those strict criteria account for the limited number of patients included.

Although subjects admitted to methadone maintenance programs have previously been selected for the clinical evaluation of the abuse potential of different opioids (Lamas et al. 1994a),this population subgroup has been very rarely selected for assessing other compounds. To our knowledge, the effects of benzodiazepines in methadone-maintained patients have been only assessed in two experimental studies (Pond et al. 1982; Preston et al. 1984, 1986). In these studies, the effects of methadone-diazepam combinations were compared to each drug administered alone. The design (concurrent administration) and objectives (assessment of drug interactions) of both studies were different from our investigation.

We believe that the effects observed after the administration of flunitrazepam and triazolam can be only attributable to the action of these drugs, although an interaction between benzodiazepines and methadone might also be present. However, a possible interaction between flunitrazepam or triazolam and methadone has not been previously described. Flunitrazepam and triazolam seem to be metabolized through cytochrome P-450 (CYP) 3A4, and they are not inhibitors or inducers of drug metabolism (Luurila et al. 1996; Schmider et al. 1996; Varbe et al. 1996).Methadone seems to be metabolized by means of CYP1A2, CYP2D6 and CYP3A4 (Eap et al. 1996, 1997; Iribarne et al. 1996), and it is known that could act as an inhibitor of CYP2D6 (Wu et al. 1993). Experimental data seem to confirm that diazepam, which is metabolized by CYP3A4 and CYP2C19 (Schmider et al. 1996), did not interact at pharmacokinetic level with methadone (Pond et al. 1982; Preston et al. 1986). Moreover, no pharmacodynamic interaction was found when diazepam was added to the usual methadone dose in patients included in a maintenance program (Preston et al. 1984). Thus, a similar result for flunitrazepam and triazolam could be expected.

Although flunitrazepam shared many effects with triazolam, it exhibited a different pharmacological profile. The mechanisms underlying these differences are unclear, but they may be related to the high affinity of flunitrazepam for the benzodiazepine receptor, its higher intrinsic efficacy, or its greater lipid solubility (Mattila and Larni 1980; Arendt et al. 1983). Flunitrazepam has a very fast absorption and seems to penetrate into the brain tissue rapidly from plasma. It has been suggested that substances with rapid brain penetration and rapid onset of effects could have a higher likelihood of drug abuse liability (Farré and Camí 1991).

The lack of previous studies assessing the abuse liability of flunitrazepam in sedative abusers prevents the comparison of our results. As commented in a recent review of the abuse liability of flunitrazepam (Woods and Winger 1997), more research is needed for a proper position of flunitrazepam in relation to other benzodiazepines. Our results may help to interpret the popularity of flunitrazepam among opioid abusers. The euphoria induced by the drug in an experimental setting in methadone-maintained patients could be a relevant factor for its abuse.

In summary, the presence of drug-induced euphoria in methadone-maintained patients after oral administration of flunitrazepam together with the epidemiological evidence of its abuse in opioid-dependent patients, suggest that flunitrazepam may be included in the group of benzodiazepines with relatively high abuse potential.

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